PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 2194
KEVIN THORNE	Group Art Unit: 1651
Serial No.: 10/606,190	Examiner: Vera Afremova
Filed: June 25, 2003	Attorney Docket: 2103.014900/RFE (SBI-129)
For: RAPID ISOLATION OF OSTEOINDUCTIVE PROTEIN MIXTURES FROM MAMMALIAN BONE TISSUE	**CUSTOMER NO. 45488**

APPEAL BRIEF

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant hereby submits this Appeal Brief to the Board of Patent Appeals and Interferences in response to the final Office Action dated August 1, 2006. The fee for filing this Appeal Brief is $500.

The Director is authorized to deduct said fee under 37 C.F.R. §§ 1.16 to 1.21 from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/2103.014900RE.

I. REAL PARTY IN INTEREST

The real party in interest is Zimmer Orthobiologics, Inc., having a place of business at 9301 Amberglen Blvd., Bldg. J, Suite 100 Austin, Texas 78729-1103.

II. RELATED APPEALS AND INTERFERENCES

None.

III. STATUS OF THE CLAIMS

Claims 1-24 are pending and are the subject of this appeal.

IV. STATUS OF AMENDMENTS

Applicant did not file any amendments after mailing of the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 relates to a process for obtaining osteogenic proteins from mammalian bone tissue (p. 6, lines 2-3). The process comprises contacting bone tissue with an acidic demineralization medium to provide demineralized bone tissue and a mineral-containing supernatant (p. 6, lines 4-5). In addition, the process comprises separating the mineral-containing supernatant from the demineralized bone tissue (p. 11, lines 18-19). Further, the process comprises removing at least part of the mineral component of the mineral-containing supernatant by contacting the mineral-containing supernatant with a mineral precipitation agent to provide a protein supernatant (p. 11, lines 19-20; p. 21, lines 18-21). The process also comprises extracting osteogenic proteins from the protein supernatant by contacting the protein supernatant with a protein extraction agent to provide an extracted protein medium (p. 6, line 24

to p. 7, line 1). Also, the process comprises recovering osteogenic proteins from the extracted protein medium (p. 7, lines 15-16).

Claim 9 relates to a method for isolating osteogenic proteins from mammalian bone tissue (p. 6, lines 2-3). The method comprises demineralizing bone tissue in an acid medium to provide demineralized bone tissue and a mineral-containing acid supernatant (p. 6, lines 4-5). Further, the method comprises separating the mineral-containing acid supernatant from the demineralized bone tissue (p. 11, lines 18-19). In addition, the method comprises removing at least a portion of the minerals from the mineral-containing acid supernatant to provide a protein supernatant (p. 11, lines 19-20). Also, the method comprises extracting osteogenic proteins from the protein supernatant with a protein extraction agent to provide an extracted protein medium (p. 6, line 24 to p. 7, line 1). The method also comprises recovering osteogenic proteins from the extracted protein medium (p. 7, lines 15-16).

Claim 24 relates to a method for isolating osteogenic proteins from mammalian bone tissue (p. 6, lines 2-3). The method comprises demineralizing bone tissue in an acid medium to provide demineralized bone tissue and a mineral-containing acid supernatant (p. 6, lines 4-5). The method also comprises separating the mineral-containing acid supernatant from the demineralized bone tissue (p. 11, lines 18-19). Further, the method comprises extracting osteogenic proteins from the mineral-containing acid supernatant with a protein extraction agent to provide an extracted protein medium (p. 6, line 24 to p. 7, line 1). In addition, the method comprises recovering osteogenic proteins from the extracted protein medium (p. 7, lines 15-16).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Are claims 1-5, 9-19, and 24 anticipated by Urist, US 4,294,753 ("Urist '753")?

Are claims 1-24 unpatentable over Urist '753, in view of Poser *et al.*, US 5,371,191 ("Poser") and Urist, US 4,619,989 ("Urist '989")?

VII. ARGUMENT

A. Patentability of claims 1- 24

1. Patentability of claims 1-5, 9-19, and 24 over Urist '753 under 35 U.S.C. §102

The Examiner alleged Urist '753 teaches a method of obtaining osteogenic proteins from mammalian bone tissue by demineralizing bone tissue in an acidic medium (col. 3, lines 1-5), extracting proteins with urea or guanidine (col. 3, lines 19-20), high and low molecular weight filtration (col. 4, lines 1-10) and further purifying extracted proteins by diafiltration with urea, precipitating minerals with calcium salts (col. 3, line 50), redissolving and reprecipitating extracted proteins (col. 3, lines 34-45), including redissolving in acid (col. 3, line 54), and lyophilization (col. 4, line 37). The Examiner also alleged Urist '753 teaches the recovery of osteogenic proteins from a supernatant hydrochloric acid solution in dialysis sacs (col. 3, lines 7-10) and that the supernatant solution is a "mineral containing supernatant."

Urist '753 at col. 3, lines 1-11, teaches the following:

Crushed bone, containing minerals, osteogenic proteins, and bone matrix, is contacted with an acidic solution in a dialysis bag (col. 3, lines 1-2);

The crushed bone and acidic solution mixture is subjected to dialysis against the same surrounding acidic solution (col. 3, lines 1-5);

Minerals diffuse from the crushed bone and acidic solution mixture into the surrounding acidic solution, leaving a mixture containing acidic solution, osteogenic proteins, and bone matrix in the dialysis bag (col. 3, lines 1-7); and

Optional extraction of osteogenic proteins from the acidic solution in the dialysis bag (col. 3, lines 9-11).

Claims 1, 9, and 24, and all claims dependent thereon, recite contacting or demineralization of bone tissue with an acidic material to yield demineralized bone tissue and a mineral-containing supernatant or mineral-containing acid supernatant; separating the supernatant from the demineralized bone tissue; and removing at least a portion of minerals from the supernatant. Urist '753 does not teach all these steps. Indeed, Urist '753 *only* teaches addition of an acidic solution to crushed bone in a dialysis bag and does *not* teach separating the supernatant from the demineralized bone tissue. The Examiner has argued that the transient production in the dialysis bag of Urist '753 of an acidic solution containing minerals and osteogenic proteins satisfies the requirement of the present claims for a separating step. However, the production of such an acidic solution containing minerals and osteogenic proteins is encompassed by the claimed contacting or demineralization step yielding a mineral-containing supernatant or mineral-containing acid supernatant and demineralized bone tissue. The separating step of claims 1, 9, and 24 requires a further action to bring the supernatant and the demineralized bone tissue out of physical adjacency. For example, in particular embodiments, the separating step can be performed by centrifugation, among other techniques (p. 16, lines 9-11). In contrast, Urist '753 does *not* bring the supernatant and the bone solids out of physical adjacency. Urist '753 instead goes directly from contacting or demineralization, yielding a supernatant, to removal of minerals from the supernatant, specifically by dialysis. Therefore, Urist '753 does not teach every element of claims 1, 9, and 24, and claims dependent thereon.

For at least the foregoing reasons, Applicant submits claims 1-5, 9-19, and 24 are patentable over and are not anticipated by Urist '753.

2. Patentability of claims 1- 24 over Urist '753 in view of Poser and Urist '989 under 35 U.S.C. §103

Urist '753 has been discussed above. The Examiner pointed to Poser as teaching protein extraction with guanidine or urea from demineralized bone matrix and further purification steps such as diafiltration to remove or replace urea for guanidine and to Urist '989 as teaching protein washing by the use of acetone. The Examiner repeated her allegation that Urist '753 teaches protein extraction from mineralized acidic supernatant. For the reasons discussed above, that allegation concerning Urist '753 is incorrect.

In addition to the teachings discussed above, Poser teaches the extraction of osteogenic proteins from demineralized bone, *not an acidic supernatant*, whether mineral-containing or not (col. 5, lines 20-22). As a result, any supplementation of Urist '753 by Poser regarding protein extraction agents or further purification steps does *not* render obvious a method containing the step of separating a mineral-containing supernatant from a demineralized bone tissue.

Urist '989, in addition to the teachings discussed above, teachings further purification steps to be performed on the product of Urist '753 (col. 1, lines 51-65) and *is silent* concerning processing steps relating to *the demineralized acidic supernatant* generated according to the teachings of Urist '753. As a result, any supplementation of Urist '753 by Urist '989 regarding acetone washing of osteogenic proteins does *not* render obvious a method containing the step of separating a mineral-containing supernatant from a demineralized bone tissue.

For at least the foregoing reasons, Applicant submits claims 1-24 are patentable over Urist '753 in view of Poser and Urist '989.

VIII. CLAIMS APPENDIX

Claims 1-24, the subject of the present appeal, are set forth in the attached "Claims Appendix."

IX. EVIDENCE APPENDIX

There is no separate Evidence Appendix for this appeal.

X. RELATING PROCEEDINGS APPENDIX

There is no Related Proceedings Appendix for this appeal.

XI. CONCLUSION

Applicant submits all pending claims 1-24 are in condition for allowance.

Respectfully submitted,

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AGENT FOR APPLICANT

CLAIMS APPENDIX

Claim 1. A process for obtaining osteogenic proteins from mammalian bone tissue comprising:

contacting bone tissue with an acidic demineralization medium to provide demineralized bone tissue and a mineral-containing supernatant;

separating the mineral-containing supernatant from the demineralized bone tissue;

removing at least part of the mineral component of the mineral-containing supernatant by contacting the mineral-containing supernatant with a mineral precipitation agent to provide a protein supernatant;

extracting osteogenic proteins from the protein supernatant by contacting the protein supernatant with a protein extraction agent to provide an extracted protein medium; and

recovering osteogenic proteins from the extracted protein medium.

Claim 2. The method of claim 1 wherein said recovering step comprises

filtering said extracted protein medium in a first ultrafiltration step using a first ultrafiltration membrane having a nominal molecular weight cutoff corresponding to a high molecular weight limit to provide a permeate comprising a first osteogenic solution;

filtering the first osteogenic solution in a second ultrafiltration step using a second ultrafiltration membrane having a nominal molecular weight cutoff corresponding to a low molecular weight limit to provide a retentate comprising a second osteogenic solution; and

purifying the osteogenic proteins in said second osteogenic solution.

Claim 3. The method of claim 2 wherein said protein extraction agent comprises guanidine hydrochloride.

Claim 4. The method of claim 3 wherein said purifying step comprises

removing said guanidine hydrochloride by at least one diafiltration step in which the osteogenic proteins are diafiltered into a diafiltration medium that does not comprise guanidine hydrochloride.

Claim 5. The method of claim 4 wherein said purifying step further comprises at least one purification operation selected from the group consisting of lyophilization and precipitation.

Claim 6. The method of claim 3 wherein said purifying step comprises

a first diafiltration step in which at least a portion of the guanidine hydrochloride is removed by diafiltering the osteogenic protein into a first diafiltration medium comprising urea, and

a second diafiltration step in which at least a portion of the urea is removed by diafiltering the osteogenic protein into a second diafiltration medium comprising dilute hydrochloric acid.

Claim 7. The method of claim 6 wherein said purifying step further comprises

lyophilizing the proteins from the second diafiltration medium to provide a solid osteogenic protein mixture.

Claim 8. The method of claim 7 wherein said purifying step further comprises

dissolving said solid osteogenic protein mixture in a first purification medium comprising dilute hydrochloric acid;

precipitating the proteins by contacting the first purification medium with a protein precipitating agent;

separating the precipitated proteins from the first purification medium and the protein precipitating agent; and

dissolving the separated and precipitated proteins in a second purification medium comprising dilute hydrochloric acid; and

lyophilizing the proteins from the second purification medium to provide solid osteogenic proteins.

Claim 9. A method for isolating osteogenic proteins from mammalian bone tissue comprising:

demineralizing bone tissue in an acid medium to provide demineralized bone tissue and a mineral-containing acid supernatant;

separating the mineral-containing acid supernatant from the demineralized bone tissue;

removing at least a portion of the minerals from the mineral-containing acid supernatant to provide a protein supernatant;

extracting osteogenic proteins from the protein supernatant with a protein extraction agent to provide an extracted protein medium; and

recovering osteogenic proteins from the extracted protein medium.

Claim 10. The method of claim 9 wherein the acid medium comprises hydrochloric acid.

Claim 11. The method of claim 9 wherein said removing step comprises contacting the mineral-containing acid supernatant with a mineral precipitation agent.

Claim 12. The method of claim 11 wherein the mineral precipitation agent comprises calcium oxalate.

Claim 13. The method of claim 9 wherein said extracting step comprises contacting said protein supernatant solution with guanidine hydrochloride.

Claim 14. The method of claim 9 wherein said recovering step comprises

filtering said extracted protein medium in a first ultrafiltration step to remove proteins having a molecular weight exceeding a desired high molecular weight limit to provide a first filtered solution;

filtering the first filtered solution in a second ultrafiltration step to remove proteins having a molecular weight below a desired low molecular weight limit to provide a second filtered solution; and

purifying the osteogenic proteins in said second filtered solution.

Claim 15. The method of claim 14 wherein said purifying step comprises removing said protein extraction agent by at least one diafiltration step in which the osteogenic proteins are transferred to a medium that does not comprise the protein extraction agent.

Claim 16. The method of claim 15 wherein said protein extraction agent comprises guanidine hydrochloride.

Claim 17. The method of claim 15 wherein said protein extraction agent comprises urea.

Claim 18. The method of claim 15 wherein said purifying step comprises a first diafiltration step in which the osteogenic proteins are transferred to a medium that does not comprise the protein extraction agent, and a second diafiltration step in which the osteogenic proteins are transferred to a dilute acid medium that does not comprise the protein extraction agent.

Claim 19. The method of claim 15 wherein said purifying step further comprises at least one purification operation selected from the group consisting of lyophilization and precipitation.

Claim 20. The method of claim 14 wherein said protein extraction agent comprises guanidine hydrochloride and said purifying step comprises

a first diafiltration step in which the guanidine hydrochloride is removed by diafiltering the osteogenic protein into a first diafiltration medium comprising urea, and

a second diafiltration step in which the urea is removed by diafiltering the osteogenic protein into a second diafiltration medium comprising dilute hydrochloric acid.

Claim 21. The method of claim 20 wherein said purifying step further comprises

lyophilizing the proteins from the second diafiltration medium to provide solid osteogenic proteins.

Claim 22. The method of claim 21 wherein said purifying step further comprises

dissolving said solid osteogenic proteins in a first purification medium comprising dilute hydrochloric acid;

precipitating the proteins by contacting the first purification medium with a protein precipitating agent;

separating the precipitated proteins from the first purification medium and the protein precipitating agent; and

dissolving the separated and precipitated proteins in a second purification medium comprising dilute hydrochloric acid; and

lyophilizing the proteins from the second purification medium to provide purified osteogenic proteins.

Claim 23. The method of claim 22 wherein said protein precipitating agent comprises acetone.

Claim 24. A method for isolating osteogenic proteins from mammalian bone tissue comprising:

demineralizing bone tissue in an acid medium to provide demineralized bone tissue and a mineral-containing acid supernatant;

separating the mineral-containing acid supernatant from the demineralized bone tissue;

extracting osteogenic proteins from the mineral-containing acid supernatant with a protein extraction agent to provide an extracted protein medium; and

recovering osteogenic proteins from the extracted protein medium.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.